Perfect timing: Making the 'switch' from juvenile to adult

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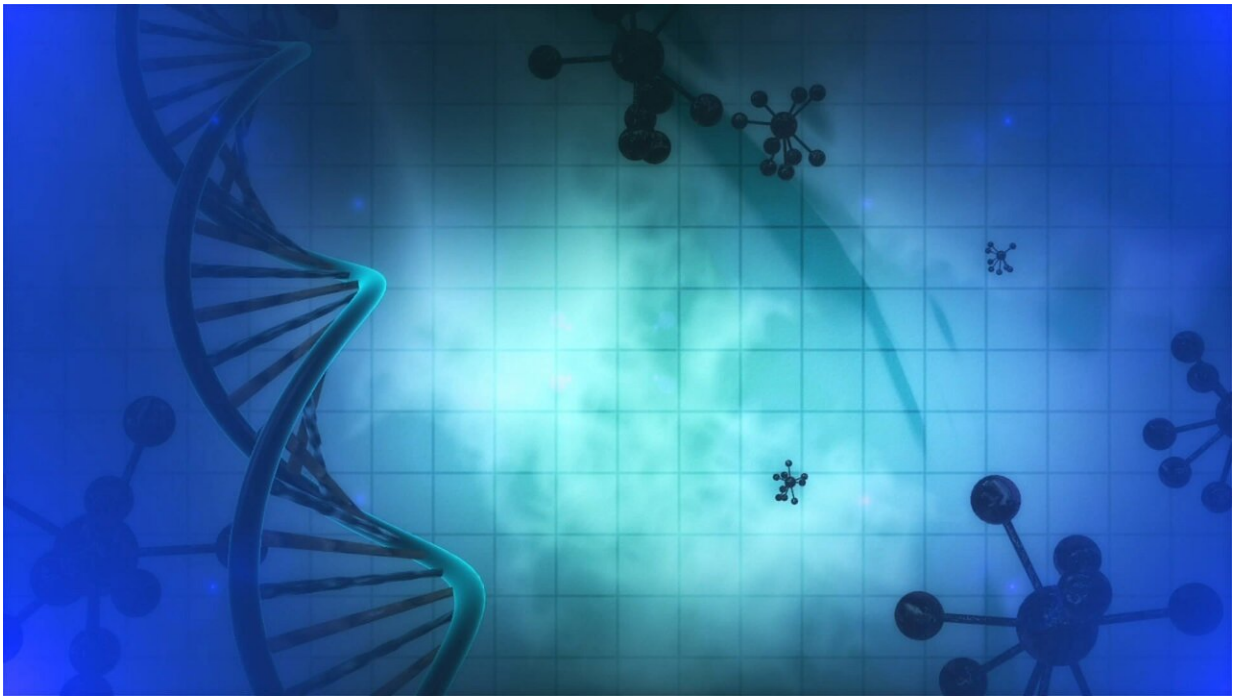

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Very little is known about how the onset of puberty is controlled in humans, but the discovery of a new gene in the roundworm *C. elegans* could be the "missing link" that determines when it's time to make this juvenile-to-adult transition. Two genes, LIN28 and MKRN3, are known to be associated with precocious puberty in humans, where juveniles as young as six may start developing adult features. These genes are found

in all animals, including *C. elegans*, in which they also control the juvenile-to-adult transition. Until the new discovery, it was unclear how these two genes are connected.

The more obvious signs of the transition of juvenile-to-adult tend to be external—body morphology, matured genitalia—but nervous system changes are also happening at the same time. In humans, the maturation of the brain during adolescence is associated with increased vulnerability to a variety of neuropsychiatric disorders, so a better understanding of these processes is important for understanding mental health as well as basic neurobiology.

Two new studies in the labs of Douglas Portman, Ph.D. at the University of Rochester Medical Center and David Fitch at New York University, published in *Developmental Cell* and *eLife*, identified a new developmental timing mechanism involving a long non-coding RNA in the microscopic roundworm *C. elegans*. Their research revealed a surprising new molecular mechanism that controls the timing of sex-specific changes in body shape, the maturation of neural circuits, and behavior.

C. elegans has long been used by researchers to understand fundamental mechanisms in biology. Many of the discoveries made using these worms apply throughout the animal kingdom and this research has led to a broader understanding of human biology. In fact, three Nobel Prizes in medicine and chemistry have been awarded for discoveries involving *C. elegans*.

The researchers identified a new gene that, when disrupted, delays the transition from the juvenile to the adult stage. Surprisingly, this gene, called lep-5, does not act as a protein, as most genes do. Instead, it functions as a long non-coding RNA (lncRNA), a recently discovered class of genes whose functions remain largely mysterious. The team

observed that this lncRNA is important for promoting the juvenile-to-adult transition by directly interacting with LIN-28 and LEP-2, a *C. elegans* gene similar to MKRN3. Because the human versions of LEP-2 and LIN-28 are both involved in the timing of puberty, the new research suggests that a yet-to-be-discovered lncRNA might be essential to this process in humans as well.

In the roundworm nervous system, some neural circuits undergo a functional transition in males as they become sexually mature adults, which is critical for generating adult-specific behaviors important for reproductive success. The male tail also undergoes a change in shape that enables mating behavior. The researchers found that this same pathway controls both the functional maturation of these circuits and the shape of the tail. Roundworms carrying mutations in lep-5 become physically mature adults, but their nervous system remains arrested in the juvenile stage, and their tails retain a juvenile form.

With respect to changes in behavior, the pathway regulates this timing by acting in the nervous system itself, not in a tissue that sends timing signals to the nervous system. Moreover, individual neurons manage their own developmental clocks. A timed "pulse" of lep-5 activity during the juvenile stage causes LIN-28 to become inactive, allowing the transition to adulthood to proceed.

Continued studies of the mechanisms identified in these studies will help scientists better understand the ways in which genetic and environmental cues regulate the transition to adulthood in humans. This research was supported by the National Institute of General Medical Sciences and National Science Foundation grants to Portman and Fitch.

More information: Hannah Lawson et al, The Makorin lep-2 and the lncRNA lep-5 regulate lin-28 to schedule sexual maturation of the C. elegans nervous system, *eLife* (2019). DOI: 10.7554/eLife.43660

Karin C. Kiontke et al. The Long Non-Coding RNA lep-5 Promotes the Juvenile-to-Adult Transition by Destabilizing LIN-28, *Developmental Cell* (2019). DOI: 10.1016/j.devcel.2019.03.003